REMARKS

STATUS OF THE CLAIMS:

Claims 1 to 40 and 42 to 52 are cancelled.

Claim 41 has been amended.

Claim 41 is pending.

Claim 41 was amended to append the phrase "inhibition of cellular proliferation by" after each of "resistant or sensitive to", "sensitivity to" and "resistance to". Support may be found in Example 1. Applicants assert that these amendments were not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 41 is reserved. No new matter has been added.

Claim 41 was further amended to append the phrase "relative to a standard" after "in said sample" in the second and third instances. Support for this amendment may be found on page 12 and in Example 1. Applicants remind the Examiner that there is no requirement for a limitation to be explicitly supported word-for-word in the specification in order for the written description requirement to be satisfied. Rather, the M.P.E.P. states that claim limitations may be supported in the specification through "express, implicit, or inherent disclosure..." and that "there is no *in haec verba* requirement" (see M.P.E.P. 2163(I)(B))(emphasis added). The M.P.E.P. teaches that whether the written description requirement is met turns on whether "...a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification...See, e.g., Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, USPQ 391, 395 (CCPA 1972)(stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient"). (see M.P.E.P. 2163(II)(A)(3)(a))(emphasis added). In the case of the claimed invention, the "standard" level of EphA2 expression is determined empirically to account for normal inter-cell variation. Applicants assert that these amendments were not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 41 is reserved. No new matter has been added.

Claim 41 was further amended to append the term "activity" after the "EphA2" term. Support for this amendment may be found on pages 4, 7-8, and 29-30. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 41 is reserved. No new matter has been added.

I. Miscellaneous

a. Objections to the Drawings

The Examiner has objected to the drawings stating:

> Figures 1 and 7 are objected to because they are not legible.
> Figure 2 is objected to because the vertical line separating panels A & B is in the wrong place.

Applicants disagree with the Examiner's objection and believe it is in error in view of Applicant's September 14, 2006 Reply in which amended Drawings were submitted to overcome the Examiner's objections to the same.

II. Rejections under 35 U.S.C. § 101

a. The Examiner has maintained the rejection of Claim 41 under 35 U.S.C. § 101 alleging it is unpatentable over Claim 16 of US Application 11/072,175 under the judicially created doctrine of obviousness-type double patenting.

Applicants respectfully disagree with the Examiner's allegation. However, Applicants note that the Examiner's rejection is "provisional", and in accordance with MPEP 804(I)(B), no action is currently required on behalf of Applicants.

III. Rejections under 35 U.S.C. § 112, Second Paragraph

a. The Examiner rejected Claim 41 under 35 U.S.C. § 112, second paragraph alleging that it is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that:

> For Claim 41, the phrases "indicative of sensitivity" and "indicative of resistance" render the claim indefinite. It is unclear whether said "sensitivity" and "resistance" means the effect of the inhibitor on EphA2 expression or the effect of the drug to treat cancer cells. Furthermore, if the meaning is the effect of the drug to treat cancer cells, it is unclear whether the effect on cancer cells is cell death, reduction of growth rate, reduction of invasiveness, or some other parameter. The skilled artisan would not know the metes and bounds of the recited invention. For purposes of examination, it is assumed that sensitivity means the inhibitor reduces growth of the breast cancer cell, while resistance means the inhibitor does not reduce growth of the breast cancer cell.

Applicants disagree with the Examiner's rejection and assert one skilled in the art would readily appreciate the meaning of a reference to a cell's sensitivity or resistance to any given compound. However, in the sole interest of facilitating prosecution, Applicants have appended the phrase "inhibition of cellular proliferation by" after each of "resistant or sensitive to", "sensitivity to" and "resistance to". Applicants believe the Examiner's rejection of Claim 41 under 35 U.S.C. § 112, second paragraph has been overcome in view of this amendment and respectfully request withdrawal of the same.

b. The Examiner rejected Claim 41 under 35 U.S.C. § 112, second paragraph alleging that it is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that:

> For Claim 41, the phrases "increased expression of... [EphA2] ...is indicative of sensitivity" and "decreased expression of... [EphA2] ...is indicative of resistance" render the claim indefinite. The art clearly taught that EphA2 is increased in breast cancer cells and can cause tumorigenesis of mammary epithelial cells (Zelinski et al, 2001). In addition, it was known that reduction of EphA2 expression inhibits growth and invasiveness of breast cancer cells (Carles-Kinch et al, 2002). Thus, the skilled artisan would have known that a drug-induced reduction of EphA2 expression would indicate sensitivity of cancer cells to the drug, while failure to reduce EphA2 expression, or an increase in expression, would indicate resistance. For these reasons, the phrases "increased expression of... [Epl-u~.2] ...is indicative of sensitivity" and "decreased expression of... [EphA2] ...is indicative of resistance" render the claim indefinite.

Applicants disagree with the Examiner's rejection and assert it is in error as being misrepresentative of the claimed invention. Specifically, the claimed invention is directed to a method of predicting whether a breast cancer cell is resistant or sensitive to a protein tyrosine kinase inhibitor based merely on the expression level of the EphA2 gene at the time the assay is performed – the claimed method does not require measuring the expression level of EphA2 in the presence of a protein tyrosine kinase inhibitor. The Examiner's basis for the rejection appears to be based upon her belief that the measurement of EphA2 expression is being performed subsequent to contact with a protein tyrosine kinase inhibitor which is not the case. While the predictor polynucleotides and

predictor polynucleotide sets were originally identified by comparing the expression profiles of both sensitive and resistant breast cancer cells subsequent to contact with a protein tyrosine kinase inhibitor, the claimed invention is not directed to the latter method. Accordingly, Applicant's respectfully request that the rejection of Claim 41 under 35 U.S.C. § 112, second paragraph be withdrawn.

c. The Examiner rejected Claim 41 under 35 U.S.C. § 112, second paragraph alleging that it is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that:

> Claim 41 recites a method wherein the effect of an inhibitor to increase or decrease expression of an EphA2 gene product is measured. However, the claim fails to define how the "increase" or "decrease" is assessed, i.e., what is compared. For example, the method might compare EphA2 expression with and without inhibitor or, alternatively, might compare the effect of inhibitor on EphA2 expression in cancer cells to expression in normal cells. The metes and bounds of the recited invention are unclear. Thus, Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite. For purposes of examination, it is assumed that the recited method compares EphA2 expression in a cancer cell with and without inhibitor.

Applicants disagree with the Examiner's rejection and assert one skilled in the art would readily appreciate the meaning of a reference to a gene's expression as being either increased or decreased. In addition, Applicants disagree with the Examiner's rejection and assert it is in error as being misrepresentative of the claimed invention. Specifically, the Examiner's rejection is based on the incorrect assumption that the "the recited method compares EphA2 expression in a cancer cell with and without inhibitor". However, the claimed invention is directed to a method of predicting whether a breast cancer cell is resistant or sensitive to a protein tyrosine kinase inhibitor based merely on the expression level of the EphA2 gene at the time the assay is performed – the claimed method does not require measuring the expression level of EphA2 in the presence of a protein tyrosine kinase inhibitor as outlined *supra*. However, in the sole interest of facilitating prosecution, Applicants have appended the phrase "relative to a standard" after "in said sample" in the second and third instances.

Accordingly, Applicant's respectfully request that the rejection of Claim 41 under 35 U.S.C. § 112, second paragraph be withdrawn in view of these amendments, in part, in addition to the arguments presented, in part.

IV. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of Claim 41 under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner alleges that:

> Claim 41 is rejected under 35 U.S.C. 112, first paragraph for lack of enablement. The specification is enabling for determining in which of the eleven breast cancer cell lines of Figure 2AUpper the pleiotropic protein tyrosine kinase inhibitor BMS-A increases or decreases expression of an EphA2-encoding mRNA. However, the specification does not reasonably provide enablement for identifying the sensitivity of any breast cancer cell to any pleiotropic inhibitor of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2 by measuring the increased expression of an EphA2 gene product. Likewise, the specification does not reasonably provide enablement for identifying the resistance of any breast cancer cell to any said pleiotropic inhibitor by measuring the decreased expression of an EphA2 gene product. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants disagree with the Examiner's maintenance of the rejection of Claim 41 under 35 U.S.C. § 112, first paragraph, and assert that the claimed invention is enabled based solely upon the teachings of the instant specification. Applicants point out that corroborating data (e.g., see the Dr. Huang Declaration submitted on September 14, 2006), and arguments in favor of the claimed invention being enabled, have already been previously set out in the record and need not be repeated.

In addition, the basis of the Examiner's rejection relating to the claimed invention encompassing the prediction of the response of "any breast cancer cell" to a protein tyrosine kinase inhibitor is believed to be in error on account of the Examiner's prior withdrawal of this basis (see December 19, 2006 Office Action, page 5). However, even if the Examiner were to have nonetheless reinstated this basis, it would not be proper on account of it failing to be consonant with the Office's treatment of other claimed diagnostic methods. In particular, the Examiner alleges that: the instant claimed method is only enabled for determining which of the eleven breast cancer cell lines illustrated in Figure 2 are sensitive or resistant. However, if this basis were to be broadly

applied, then any diagnostic method that seeks to make a prediction based upon an unknown patient sample, or any other sample or cell line not disclosed in the specification, could be found to not be enabled for failure to disclose the sample in the specification. Clearly such a basis does not purport with patent law nor judicial precedent. Rather, Applicants point out that the patent law merely requires that the specification describe the invention sufficiently to enable a skilled artisan to "make and use" the invention. The specification's demonstration that the predictor polynucleotides, including the EphA2 receptor polynucleotides and polypeptides, can accurately predict which of the eleven breast cancer cell lines illustrated in Figure 2 and listed in Table in bold, are sensitive or resistant to a protein tyrosine kinase inhibitor is sufficient to satisfy the enablement requirement.

Furthermore, Applicants assert that the rejection of Claim 41 is improper on the basis that the Examiner has failed to meet her burden in establishing that one skilled in the art would not know how to make and use the invention embraced by these claims. Applicants point out that the "test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." (MPEP 2164.01). In establishing a reasonable basis for rejecting a claim for lack of enablement, the Examiner must make "specific findings of fact, supported by the evidence, and then draw[] conclusions based on these findings of fact" (MPEP 2164.04) - the "examiner should **never** make the determination based on personal opinion." (MPEP 2164.05).

Applicants reassert that the test for enablement is whether the claimed invention is described in such a way as to enable any person skilled in the art "to make or use the invention from the disclosures in the patent coupled with information in the art without undue experimentation". See *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). In addition, the MPEP states the fact that "experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation". MPEP 2164.01; *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). As established *supra* and elsewhere in the record, the specification teaches that EphA2 expression is a reliable predictor of whether a breast cancer cell is predicted to be sensitive or resistant to a protein tyrosine kinase inhibitor, which has been corroborated by additional evidence as shown in the Dr. Huang Declaration. Thus, a skilled artisan would not require undue experimentation to practice the invention encompassed by Claim 41 because the skilled artisan would only need to practice the claimed method based upon the teachings of the specification as

originally filed. In addition, measuring expression levels of an informative gene in a patient sample for diagnostic purposes is routine in the art and clearly would not require undue experimentation.

In addition, the Examiner's basis does not appear to be consonant with the claimed invention on the ground she appears to be treating the invention as being directed to a genus of cell lines, as opposed to a diagnostic method of predicting which cell is sensitive or resistant to a protein tyrosine kinase inhibitor. As the language of Claim 41 clearly provides, the invention is not directed to a genus of breast cancer cell lines. While Applicant's utilized a panel of breast cancer cell lines to assist in the conception of the invention, that mere fact should not negate the utility of the invention to merely diagnosing those cell lines actually tested. Rather, the fact that at least 11 breast cancer cell lines was used actually demonstrates that the invention is enabled and works for its intended purpose by accurately predicting which cell lines were resistant and sensitive to a protein tyrosine kinase inhibitor.

Regarding the Examiner's allegation that the specification is not enabled for predicting the sensitivity of any pleotropic inhibitor, Applicants disagree and assert the Examiner's basis for this rejection is in error on the ground it is not representative of the claimed invention. First, the claimed invention is directed to a method of predicting whether a breast cancer cell is resistant or sensitive to a protein tyrosine kinase inhibitor based merely on the expression level of the EphA2 gene at the time the assay is performed – the claimed method does not require measuring the expression level of EphA2 in the presence of a protein tyrosine kinase inhibitor. However, the Examiner's basis for the rejection appears to be based upon her belief that the measurement of EphA2 expression is being performed subsequent to contact with a protein tyrosine kinase inhibitor which is not the case. Secondly, the Examiner incorrectly bases this rejection on the requirement that EphA2 serve as a marker for "every cancer cell". Applicants assert this basis is in error because the claimed invention merely entails the use of the EphA2 receptor in breast cancer cells, and not "every cancer cell". Thirdly, the Examiner uses the term "and/or" and phrase "one or more of" throughout the Action in reference to the "Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2" limitation of Claim 41 which is not correct. Specifically, Applicants specifically amended Claim 41 to remove the "one or more" language previously (see amendment to Claim 41 in Applicant's May 16, 2007 Reply). Fourth, the Examiner's allegations regarding the art teaching away from the use of EphA2 expression as an indicator of breast cancer is not applicable to the claimed invention because neither Zelinski et al., nor Carles-Kinch et al. teach the use of the method currently claimed. As it

relates to the claimed invention, the use of the EphA2 expression levels is only relevant for predicting whether a breast cancer cell will be sensitive or resistant to a protein tyrosine kinase inhibitor, in which the inhibitor Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2. Knowledge in the art regarding the use of EphA2 expression for other purposes is irrelevant to the invention currently claimed. Lastly, the Examiner's basis does not appear to be consonant with the claimed invention on the ground she appears to be treating the invention as being directed to a genus of compounds, as opposed to a diagnostic method of predicting which cell is sensitive or resistant to a protein tyrosine kinase inhibitor. As the language of Claim 41 clearly provides, the invention is not directed to a genus of compounds.

Accordingly, Applicants believe the Examiner's rejection of Claim 41 under 35 U.S.C. § 112, first paragraph, has in error and should be withdrawn.

III. Rejections under 35 U.S.C. § 112 – First Paragraph

a. The Examiner has maintained the rejection of Claim 41 under 35 U.S.C. § 112, first paragraph alleging:

> Claim 41 is directed to a genus of methods wherein, upon treatment with any pleotropic inhibitor of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, increased expression of EphA2 is indicative of sensitivity of breast cancer cells to the inhibitor, while decreased expression of EpiC2 is indicative of resistance of breast cancer cells to the inhibitor. The specification fails to provide any example of sensitive cells wherein, increased expression of EphA2 is correlated to an effect of the inhibitor to reduce growth of the breast cancer cell. Likewise, the specification fails to provide any example of resistant cells wherein, decreased expression of EphA2 is correlated to an effect of the inhibitor to fail to decrease growth of the breast cancer cell. Given this lack of description of representative species encompassed by the genera of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants disagree with the Examiner's maintenance of the rejection of Claim 41 under 35 U.S.C. § 112, first paragraph, and assert that the claimed invention provides sufficient description to establish that Applicants were in possession of the claimed invention as outlined elsewhere in the record and corroborated by the Dr. Huang Declaration. Specifically, Applicants point out that

EphA2 was specifically identified as being the top predictor out of all 137 predictor genes outlined in Table 2 for predicting whether a breast cancer cell would be resistant or sensitive to a protein tyrosine kinase inhibitor. Table 2 clearly lists EphA2 as being highly expressed in sensitive breast cancer cells (see second column), and clearly lists EphA2 as being inhibited by BMS-A, a protein tyrosine kinase inhibitor. Each of the latter are demonstrated in Figure 2. Thus, contrary to the Examiner's allegation, the specification expressly demonstrates sensitive cells having increased expression of EphA2 which correlates to an effect of the inhibitor to reduce growth of the breast cancer cell. Clearly, one skilled in the art would recognize that Applicants were in possession of a method of using EphA2 to predict which breast cancer cells are resistant or sensitive to a protein tyrosine kinase inhibitor as a consequence of the teachings of the specification. Accordingly, Applicants believe the Examiner's rejection of Claim 41 under 35 U.S.C. § 112, first paragraph, is in error and should be withdrawn.

IV. Rejections under 35 U.S.C. § 103

a. The Examiner has maintained the rejection of Claim 41 under 35 U.S.C. § 103(a) over Kassenbrock et al, 2002 in view of Wang et al, 2002 and further in view of Ogawa et at, 2000. More particularly, the Examiner alleges:

> Examiner's note: In the interest of compact prosecution, this rejection is based on the assumption that, for the recited method, the effect of an inhibitor to decrease EphA2 expression in a cancer cell correlates with inhibition of the cancer cell's growth, i.e., sensitivity.
>
> Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kassenbrock et al, 2002 in view of Wang et al, 2002 and further in view of Ogawa et al, 2000 or Zelinski et al, 2001. Kassenbrock et al teach that, in a human breast cancer ceil line, the Src-class tyrosine kinase inhibitor PPl inhibits Cbl phosphorylation (Fig 6) and EGF-R ubiquitination (Fig 8) leading to the proposal that phosphorylation of Cbl by a Src-class kinase leads to ubiquitination and down-regulation of the EGF-R (pg 24974; parg 8). Kassenbrock et al do not teach that PPI regulates the expression level of EphA2. Wang et al teach that Cbl down-regulates EphA2 (Fig 2). Based on said teachings, a person of ordinary skill in the art would believe that, more likely than not, PP 1 by inhibiting Cbl phosphorylation would also down-regulate EphA2. Both Ogawa et al (Table 1) and Zelinski et al (Fig 1) teach that EphA2 is highly expressed in breast cancer cells. Zelinski et al further teach that over expression of EphA2 causes malignant transformation of mammary epithelial cells (Fig

> 3 & 4). Thus, based on the combined teachings of Kassenbrock et al, Wang et al, Ogawa et al, and Zelinski et al the skilled artisan would believe that, more likely than not, down-regulation of EphA2 by PP1 would inhibit tumor growth and survival. It would have been obvious to a person of ordinary skill in the art to use the method of Kassenbrock et al to test the effect of PP1 on EphA2 expression levels in breast cancer cells and to conclude that, if EphA2 was down-regulated by PP1, the cancer cell growth would be inhibited by treatment with PP1. Motivation to use said methods derives from the desire to determine ifPP1 would be successful for treatment of a patient with breast cancer. The expectation of success is high, as high levels of EphA2 are predictive of tumor growth and the art teaches that, more likely than not, PP1, via inhibition of Cbl phosphorylation, would down-regulate EphA2. Therefore, Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kassenbrock et al, 2002 in view of Wang et al, 2002 and further in view of Ogawa et al, 2000.

Applicant's disagree with the Examiner's basis for maintaining the rejection of Claim 41 under 35 U.S.C. § 103(a) and assert it is in error. First, Applicants assert that the Examiner's rejection is in error on account of it being based on an improper understanding of the currently claimed in invention. Specifically, the Examiner's rejection is based on the incorrect belief that the claimed invention requires measuring the effect of a protein tyrosine kinase inhibitor on EphA2 expression levels subsequent to the administration of such an inhibitor ("It would have been obvious to a person of ordinary skill in the art to use the method of Kassenbrock et al to test the effect of PP1 on EphA2 expression levels in breast cancer cells and to conclude that, if EphA2 was down-regulated by PP1, the cancer cell growth would be inhibited by treatment with PP1"; see page 12 of Action). However, the instant invention is directed to methods of **predicting** whether breast cancer cells will be sensitive or resistant to a protein tyrosine kinase inhibitor by measuring EphA2 expression levels. As a result, it is clear that the claimed invention is prognostic in nature, and does not involve measuring EphA2 expression levels subsequent to the administration of a protein tyrosine kinase inhibitor as alleged by the Examiner. Accordingly, because neither Kassenbrock et al, Wang et al, 2002 nor Ogawa et at, 2000 teach the elements of the claimed invention, either alone or in combination, the Examiner's rejection of Claim 41 under 35 U.S.C. § 103(a) is improper and should be withdrawn.

Secondly, Applicants point out that the Examiner has failed to cite any reference that demonstrates that PP1 is an inhibitor of each one of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, as required by the claims. Specifically, Hanke et al., merely

demonstrates that PP1 is an inhibitor of Lck, FynT, Src, and Hck, but does not demonstrate that PP1 is capable of inhibiting Fgr, Yes, Blk, Lyn, BCR-ABL, PDGFR, c-Kit, nor EphA2. While the Examiner states that PP1 was identified as a Src family kinase inhibitor and cites Hanke et al. to apparently support her incorrect allegation that PP1 also inhibits other members of this family, it is important to point out to the Examiner that the mere statement that a compound inhibits Src family kinases does not mean that the compound inhibits all members of the family. The latter may be illustrated by Hanke et al. directly in which it generally states PP1 is an inhibitor of Src family kinases, but merely shows inhibition of four of the family members.

The Examiner cites Waltenberger et al. to demonstrate that PP1 inhibits PDGF-R, and Tatton et al. to demonstrate that PP1 inhibits Kit and BCR-ABL. However, the combination of Walternberger et al., Tatton et al., and Hanke et al., fails to demonstrate that PP1 is an inhibitor of Fgr, Yes, Blk, Lyn, , and EphA2.

Additionally, the points to Kassenbrock et al. and Wang et al. to support her incorrect allegation that PP1 inhibits EphA2. In particular, these publications merely support the Examiner's tenuous inference that Src inhibition can lead to the inhibition of EphA2 expression, but neither of these references teaches that PP1 is an actual inhibitor of EphA2. In summary, none of the references cited by the Examiner, either alone or in combination, establishes that PP1 is capable of inhibiting Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2. According, the Examiner has failed to meet her burden and Applicants assert the rejection of Claim 41 under 35 U.S.C. § 103(a) is improper and should be withdrawn.

However, in the sole interest of facilitating prosecution, Applicant's have amended Claim 41 to append the term "activity" immediately after "EphA2".

Applicants believe that all of the Examiner's rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

A one-month extension is hereby requested pursuant to 37 CFR §1.136(a). Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $120 for payment of the extension fee.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already

accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,

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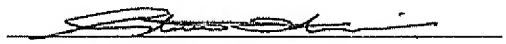

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